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Association of serum HIF-1α levels with mortality and ICU admission in hospitalized patients with SARS-CoV-2 infection: a prospective cohort study

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ABSTRACT

Aims: SARS-CoV-2 infection can trigger a dysregulated immune response, including cytokine storm syndrome (CSS), which exacerbates respiratory failure through heightened pro-inflammatory mediators and hypoxemia. Hypoxia-inducible factor-1α (HIF-1α) orchestrates cellular adaptation to hypoxia by shifting metabolism toward glycolysis. Prior studies present varying evidence regarding HIF-1α's role in acute inflammatory states. The purpose of this study was to investigate the role of hypoxia-inducible factor 1a (HIF-1a) in predicting mortality, ward and intensive care unit (ICU) admission requirements.

Methods: The study was performed as a single center prospective study in a tertiary center. Hospitalized patients with at least one positive nasopharyngeal COVID-19 reverse transcription-polymerase chain reaction test were included in the study. White blood cell count, thrombocyte count, lactate levels, fibrinogen, D-dimer, brain natriuretic peptide (BNP), C-reactive protein (CRP), procalcitonin, ferritin, interleukin 6 (IL-6) troponin, partial oxygen, and partial carbon dioxide pressure from arterial blood gas sampling were recorded.

Results: Of 127 screened, 80 participants completed the study (mean age 66.1±17.2 years; 54% male). Thirty-day mortality was 21.3% (n=17). Median BNP (529 vs. 1,957 pg/ml), ferritin (256 vs. 598.5 ng/ml), and IL-6 (14 vs. 101 pg/ml) were significantly higher in non-survivors (p=0.043, 0.003, and 0.001, respectively). Survivors exhibited lower median HIF-1α (0.85 vs. 1.20 ng/ml), but this difference was not statistically significant (p>0.05). Subgroup analyses by CURB-65 and ICU status similarly revealed no significant HIF-1α differences. HIF-1α did not correlate with any inflammatory markers. HIF-1α levels at admission did not significantly predict ICU care or mortality. This may reflect HIF-1α's pro- and anti-inflammatory roles and variability in sampling timing relative to disease onset. Current literature suggests both protective and detrimental HIF-1α effects, complicating its prognostic utility.

Conclusion: Admission HIF-1α alone does not predict clinical outcomes in hospitalized COVID-19. Studies incorporating serial measurements and baseline controls are warranted to evaluate HIF-1α's involvement in COVID-19 pathophysiology.

Keywords: Critical care, coronavirus, hypoxia, mortality

INTRODUCTION

SARS-CoV-2 belongs to the family of coronaviruses, which are responsible for infections in both humans and a wide range of animal species, and is the causative agent of Coronavirus Disease 2019 (COVID-19). As seen in the COVID-19 situation, cross-species infection can lead to a pandemic. At the time of this study, vaccination and prevention appeared to be the only viable approaches, with no specific treatments in sight. Currently, many drugs have been repurposed to treat COVID-19, including antiviral therapies for human immunodeficiency virus, monoclonal antibodies, and immunosuppressive regimens.[1,2]

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The mortality and morbidity of COVID-19 are often caused by respiratory system infections and associated complications. This is further exaggerated by the presence of cytokine storm syndrome (CSS) in certain patients, which causes an unprecedented increase in pro-inflammatory markers, including tumor necrosis factor-alpha (TNF-a) and interleukin-1 beta (IL-1b).[3] From a clinical perspective, CSS presents with fever, organ failure, and tachypnea, with respiratory failure and hypoxemia being the most severe symptoms.[4,5] A shift in favor of alternative pathways for ATP production in hypoxia is necessary in patients with CSS, and hypoxia-inducible factor 1α (HIF-1α) plays a role in this transition to a hypoxic state. HIF-1α contributes to the shift in energy production to alternative pathways, causing increased activity of the glycolytic pathway and glucose-carrying mechanisms to compensate for the overall reduction in ATP production in hypox conditions.[6,7]

Hypoxemia in itself has been an important aspect of patient management, regardless of an underlying cause. While clear approaches and treatment modalities have been established, depending on the cause, the degree of tissue damage caused by hypoxia or any parameters that may predict this damage remains a topic that requires further study. Definitions of hypoxia and hypoxemia are often used interchangeably and often present together, albeit that may not be necessary in all cases.[8,9] Hypoxemia is defined as a condition with partial oxygen in arterial blood below normal values, while hypoxia is the failure of oxygenation at the cellular level. Hypoxemia often leads to hypoxia; however, in cases where the patient is compensated for low delivery of oxygen, this may not be observed. In cases of COVID-19, both respiratory and cardiac functions may be affected; as such, hypoxemia and hypoxia may be present in different stages.[10]

The role of HIF-1a in regulating hypoxemia is a subject of investigation, with more than 100 reported genes upon which HIF-1 has a regulatory effect.[11] The degree of this modification in acute cases, such as COVID-19 infection, requires clarification, as current studies report varying results. Some studies suggest a protective role for HIF-1α activation, while others indicate a correlation with other inflammatory markers, such as IL-6.[12-14] The study hypothesized that an elevation in HIF-1 levels predicts an increased inflammatory system burden and reflects the severity of respiratory failure. Our study investigated the association between HIF-1 levels and clinical outcomes, such as mortality and intensive care unit (ICU) admission, among patients infected with COVID-19.

METHODS

This study was conducted as a single-center prospective study in a tertiary care hospital and approved by the Clinical Researches Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision No: 111/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was received in writing and orally from all patients who participated in the study. This was witnessed by at least one additional medical doctor and one relative who did not participate in the study. Mortality and survival were evaluated from the national COVID-19 database after a follow-up period of one month.

The study group consisted of patients admitted to a tertiary care hospital with COVID-19 infection between June 1, 2021, and September 1, 2021. Baseline characteristics and clinical outcomes were recorded from initial admission evaluation and the hospital patient system. The patient admissions between the mentioned dates continued until the required patient count was reached.

Blood sampling for HIF-1 serum levels was performed in addition to routine blood tests for initial COVID-19 evaluation. The sampling was performed after confirmation of COVID-19 positivity and was done within the first day of hospital admission. These samplings were collected early in the morning after a minimum of 10 hours of fasting, immediately centrifuged for 15 minutes at 1000×g, and the serum was stored at -80 °C in aliquots until the day of analysis. Serum HIF-1A level was measured using a quantitative enzyme-linked immunoassay technique (ELISA), according to manufacturer's indications (Bioassay Technology Laboratory, Zhejiang, China).

Patients aged ≥18 years, reverse transcription polymerase chain reaction test positive, and admitted through the emergency department were accepted as the study population. Those with former hospitalization histories and/or diagnosed with COVID-19 at another ward were not accepted as candidates.

Other exclusion criteria included refusal to participate, treatment with immunosuppressive agents (regardless of the disease origin), and a history of supplementary vitamin use (due to a possible anti-inflammatory effect). Overall, these additional treatment and support regimens could have affected HIF-1a levels and thus had to be excluded. Patients with known comorbidities that might have caused an increase in HIF-1a levels were also excluded from the study, including those with a history of coronary heart disease, renal failure (regardless of dialysis status), and chronic obstructive pulmonary disease.

White blood cell count, thrombocyte count, lactate levels, fibrinogen, d-dimer, brain natriuretic peptide (BNP), C-reactive protein (CRP), procalcitonin, ferritin, interleukin 6 (IL-6) troponin, partial oxygen, and partial carbon dioxide pressure from arterial blood gas sampling were recorded from routine blood tests in the hospital system and medical records.

ICU admission and mortality at day 30 were accepted as primary outcome parameters. The aforementioned inflammatory markers (CRP, lactate levels, IL-6, ferritin, and procalcitonin) were used along with CURB-65 pneumonia severity scoring to validate the need for ICU admission and mortality. Patients with ICU admission requirements were evaluated by a responsible emergency medicine specialist, according to clinical status, at the emergency ward and were transported to the ICU unit if accepted.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to evaluate the distribution of the parameters. For categorical variables,

Chi-square and Fisher-Exact tests were used. For continuous parameters, depending on the distribution, independent samples T-tests or Mann-Whitney U test were used. Subgroup analysis was planned if a statistically significant parameter was observed in the overall group evaluation. A p-value less than 0.05 was to be accepted as statistically significant. International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 30 was used as the statistical analysis program. The power analysis for the study was performed to estimate the patient requirement, in which to distinguish a difference between means of two independent groups, with a power of 0.8, type 1 error of 0.5% and effect size of 0.6, at least 72 patients were required. The effect size was chosen as to represent a moderate effect of HIF-1a, and evaluate if such an effect was present.

Considering at least 10% patient loss in the evaluation with inadequate data or later refusal to participate, a total patient count of 80 was planned with an upper limit of 90 patients were being deemed acceptable due to varying mortality rates. A subgroup analysis regarding comorbidities and age was not planned, due to exclusion criteria and the assumption of average age being at least 65 years.

RESULTS

Ninety patients (n=90) were enrolled during the first month. To reach this number, a total of 127 patients were evaluated. The remaining 37 (29%) patients were excluded from the study due to an unknown history of supplementary vitamin usage, improper blood sampling techniques, severe medical conditions unsuitable for informed consent, and refusal to participate. An additional ten patients (11%) were later excluded from the study due to missing data and/or their requests to be removed, resulting in a total sample of 80 participants.

The average age of the patients was 66.1 (±17.2) years. 37 (46%) of the sample group were female, and the rest, 43 (54%), were male. One-month mortality was observed in 17 (21.3%) of the patients. Less than half of the patients (n=36, 45%) had been diagnosed with hypertension, followed by asthma (n=10, 12.5%) and malignancy (n=6, 7.5%) as the second and third most commonly observed comorbidity. Neurologic (n=4, 5%) comorbidities were limited, and two patients (2.5%) had atrial fibrillation. Half of the patients were vaccinated for COVID-19. Regarding admission evaluation, mean arterial pressure (MAP), pulse rate, and body temperature were within normal ranges (a mean of 93.70 mmHg, 92.12 bpm, and 36.77 °C, respectively), while desaturation was present in both groups in terms of mortality (a mean of 86.53% at room air). The respiration rate was slightly elevated in both groups (a mean of 21.57 per minute). Mortality did not vary according to comorbidities and admission vitals (**Table 1**).

Regarding laboratory evaluation, WBC, PLT, and arterial blood gas sampling results, which included lactate, pH, PO_2, and PCO_2, did not differ between groups in terms of mortality. Similarly, while elevated at a mean of 527.8 (±116.56) mg/dl, fibrinogen levels were similar between groups. Other inflammatory parameters and cardiac markers were found to have non-parametric distribution. Median values of BNP (529 to 1957 pg/ml), ferritin (256 to 598.5 ng/ml), and IL-6 (14 to 101 pg/ml) were higher in the mortality group compared to the survivors (p values of 0.043, 0.003, and 0.001 respectively). Other markers, including high-sensitivity cardiac troponin (hs-ctn), D-dimer, procalcitonin, and CRP, while higher in the mortality group, did not show a statistically significant difference. HIF-1α was lower in the survivor group compared to the mortality group (1.2 to 0.85 ng/ml), but the difference was statistically insignificant (**Table 2**).

Regarding admission evaluation, the CURB-65 score was observed to be a statistically relevant parameter in mortality, with a cutoff of 2 being statistically significant in evaluating patients with mortality (p value of 0.027). Admission localization was in favor of ICU among patients in the mortality group (p-value of 0.001), while tomography findings did not differ between groups (p-value of 0.682) (**Table 3**).

Parameters were then evaluated according to the distribution among patients with a CURB-65 score of 2 or higher, to those with a score lower than 2. In this analysis; BNP, Troponin and procalcitonin were observed to be lower among CURB-65 score <2 group (p value of 0.007, 0.001 and 0.002 respectively). The same analysis was performed regarding admission localization, and BNP, procalcitonin, CRP, and ferritin were observed to be higher in the group requiring ICU admission (P value of 0.005, 0.038, 0.037, and 0.021 respectively). In both analyses, HIF-1a levels did not vary between groups (**Table 4**).

Correlation between inflammatory markers were performed to investigate any additional role of HIF-1a, however, no correlation between HIF-1a and other parameters were observed, while additional correlations between inflammatory markers were present, with BNP being correlated with troponin and D-dimer (r=0.559 and 0.464, p:0.001 for both values), troponin being corelated with D-dimer and procalcitonin (r=of 0.411, 0.307 and p value of 0.001, 0.007 respectively), procalcitonin being correlated with D-dimer, CRP and ferritin (r=0.342, 0.469 and 0.278 and p=0.003, 0.001 and 0.018 respectively) and ferritin being correlated with IL-6 (r=0.294 and p value of 0.013) (**Table 5**).

DISCUSSION

HIF-1a levels were observed to not statistically differ according to mortality, ward or ICU admission, albeit lower in the survival group. BNP, ferritin, and IL-6 levels had a significant difference regarding mortality. However, a correlation between these parameters and HIF-1a levels were not observed. Similarly, a correlation between additional inflammatory markers that had varied regarding ICU admission, CRP, and procalcitonin did not correlate with HIF-1a. Despite an acceptable patient distribution and expected pattern of other inflammatory markers regarding their role in ICU admission and mortality, no correlation or difference in HIF-1a was observed. Currently available studies regarding the evaluation of other acute inflammatory statuses do support similar predictive roles of inflammatory markers; however, due to the varying conditions, investigation of HIF-1a remains a limited aspect of investigation.[15,16]

In human peripheral blood cell studies, it was hypothesized that HIF-1a acted as an inducer of the pro-inflammatory

Table 1. Demographic parameters, comorbidities, and admission vitals

Parameters (n, %)		Survivor (n=63)	Non-survivor (n=17)	Total (n=80)	p value
Gender	Male	33 (52.4)	10 (58.8)	43 (53.8)	0.636
	Female	30 (47.6)	7 (41.2)	37 (46.2)	
Age (mean, SD, years)		64.61 (18.42)	71.64 (13.95)	66.11 (17.72)	0.096
Hypertension	Present	28 (44.4)	8 (47.1)	36 (45)	0.848
	Absent	35 (55.6)	9 (52.9)	44 (55)	
Asthma[1]	Present	8 (12.7)	2 (11.8)	10 (12.5)	0.642
	Absent	55 (87.3)	15 (88.2)	70 (87.5)	
Malignancy[1]	Present	4 (6.3)	2 (11.8)	6 (7.5)	0.602
	Absent	59 (93.7)	15 (88.2)	74 (92.5)	
Neurological comorbidities[1]	Present	3 (4.8)	1 (5.9)	4 (5)	0.623
	Absent	60 (95.2)	16 (94.1)	76 (95)	
Atrial fibrillation[1]	Present	2 (3.2)	0 (0)	2 (2.5)	0.618
	Absent	61 (96.8)	100 (100)	78 (97.5)	
COVID-19 vaccination (%)	No	31 (49.2)	9 (52.9)	40 (50)	0.785
	Vaccinated	32 (50.8)	8 (47.1)	40 (50)	
Mental status (%)	Normal	53 (84.1)	12 (70.6)	65 (81.2)	0.204
	Altered	10 (15.9)	5 (29.4)	15 (18.8)	
Mean arterial pressure (mmHg)		94.57 (15.10)	90.53 (13.78)	93.70 (14.83)	0.303
Pulse rate (bpm)		92.33 (15.22)	91.35 (12.40)	92.12 (14.60)	0.808
Body temperature (°C)		36.76 (0.75)	36.78 (0.61)	36.77 (0.71)	0.965
Oxygen saturation (%)		86.73 (10.4)	85.76 (8.82)	86.53 (9.75)	0.717
Respiration rate (/min)		21.65 (2.80)	21.29 (1.72)	21.57 (2.60)	0.62

SD: Standard deviation, 1Fisher Exact Test was used for comparison

Table 2. Comparison of laboratory parameters between survivor and non-survivor groups

Parameters (mean, SD)[1]	Survivor (n=63)	Non-survivor (n=17)	Total (n=80)	p value
WBC (10^9/L)	8.72 (3.92)	10.93 (5.13)	9.20 (4.27)	0.069
PLT (10^9/L)	222.30 (85.20)	254.52 (138.98)	229.24 (99.08)	0.374
Lactate (mmol/L)	2.14 (1.08)	2.26 (0.61)	2.16 (1.01)	0.665
pH	7.37 (0.09)	7.36 (0.08)	7.37 (0.09)	0.607
PO_2 (mmHg)	78.68 (12.41)	74.8 (10.27)	77.91 (12.06)	0.266
PCO_2 (mmHg)	40.96 (11.04)	41.16 (12.44)	41.00 (11.26)	0.951
Fibrinogen (mg/dl)	516.40 (114.78)	574.13 (116.01)	527.8 (116.56)	0.086
Parameters (median, 25-75th percentile)[2]				
BNP (pg/ml)	529 (91-1490.5)	1957 (570-4930)	714 (103.4-2097)	0.043
Hs-cTn (ng/ml)	16.42 (5.98-32.03)	20.9 (9.03-61.64)	17.53 (6.28-34.45)	0.198
D-dimer (mcg/ml)	0.97 (0.47-1.89)	1.05 (0.47-2.40)	0.97 (0.47-1.89)	0.466
Procalcitonin (ng/ml)	0.08 (0.06-0.23)	0.24 (0.07-0.39)	0.1 (0.06-0.28)	0.067
CRP (mg/dl)	73.43 (37.44-139.65)	91.95 (59.6-124.29)	76.88 (43.01-139.65)	0.249
Ferritin (ng/ml)	256 (102-520)	598.5 (339.5-767)	310 (136-564)	0.003
IL-6 (pg/ml)	14 (7.5-25)	101 (66.3-145)	17.1 (9-51)	0.001
HIF-1a (ng/ml)	1.2 (0.38-1.97)	0.85 (0.41-1.30)	1.17 (0.39-1.72)	0.129

SD: Standard deviation, WBC: White blood cell, PLT: Platelet, BNP: Brain natriuretic peptide, Hs-Ctn: High sensitivity cardiac troponin, CRP: C-reactive protein, IL-6: Interleukin-6, HIF-1a: Hypoxia-inducible factor 1-alpha; Lactate, Ph, PO_2 and PCO_2 were recorded from arterial blood gas sampling. [1]Independent samples T test was used for comparison between groups. [2] Mann-Whitney U test was used for comparison between groups

Table 3. Radiological imaging, pneumonia scoring, and admission localization

Parameters (n, %)		**Survivor** (n=63)	**Non-survivor** (n=17)	**Total** (n=80)	p value
Tomography findings consistent with COVID-19	None	12 (19)	4 (23.5)	16 (20)	0.682
	Present	51 (81)	13 (76.5)	64 (80)	
CURB-65 score	<2	41 (65.1)	6 (35.3)	47 (58.8)	0.027
	≥2	22 (34.9)	11 (64.7)	33 (41.3)	
Admission localization	Ward	49 (77.8)	4 (23.5)	53 (66.3)	0.001
	ICU	14 (22.2)	13 (76.5)	27 (33.8)	

ICU: Intensive care unit

Table 4. Cardiac and inflammatory markers comparison according to CURB-65 and admission localization

CURB-65 score		**Mean rank**	**Z score**	**p value**
Brain natriuretic peptide	<2	32.46	2.698	0.007
	≥2	46.32		
Troponin	<2	28.12	5.463	0.001
	≥2	56.76		
D-dimer	<2	33.8	1.501	0.133
	≥2	41.34		
Procalcitonin	<2	32.44	3.055	0.002
	≥2	48.22		
CRP	<2	38.18	0.147	0.883
	≥2	38.94		
Ferritin	<2	37.08	0.449	0.654
	≥2	39.38		
Interleukin-6	<2	36.09	0.703	0.482
	≥2	39.69		
HIF-1a	<2	41.59	-0.726	0.468
	≥2	37.79		
Admission localization				
Brain natriuretic peptide	Ward	32.95	2.838	0.005
	ICU	48.1		
Troponin	Ward	38.65	0.466	0.641
	ICU	41.19		
D-dimer	Ward	35.22	1.057	0.29
	ICU	40.87		
Procalcitonin	Ward	35.24	2.072	0.038
	ICU	46.28		
C-reactive protein	Ward	35.02	2.087	0.037
	ICU	46.52		
Ferritin	Ward	34.02	2.306	0.021
	ICU	46.46		
Interleukin-6	Ward	34.36	1.869	0.062
	ICU	44.46		
HIF-1a	Ward	42.08	-1.158	0.247
	ICU	35.73		

Statistical analysis between groups was made by Mann Whitney U Test due to nonparametric distribution. CRP: C-reactive protein, HIF-1a: Hypoxia-inducible factor 1-alpha, ICU: Intensive care unit, Z score: Standardized test statistic

system, as was discussed earlier.[17] However, as stated in Palazon et al.'s[18] study, HIF-1a also has regulatory roles depending on the cell being under hypoxia that may reduce a TNF-a-related inflammatory response. As such both pro and anti-inflammatory roles of HIF-1a has been reported. Early dysregulation of HIF-1a has been suggested as a trigger for inflammatory response.[13,14,18] However, HIF-1a elevation has also been reported to decrease Angiotensin-converting enzyme (ACE) receptors.[19] This effect may limit the possibility of preemptive HIF-1α inhibition in patients with COVID-19, as it would prevent the reduction of ACE receptors, thereby providing the virus with more accessible entry routes. Overall, these pathways and differing roles of HIF-1a in both pro and anti-inflammatory roles may contribute to the lack of correlation between HIF-1a and other inflammatory markers in the study, as despite standardized sampling time, an exact time of HIF-1a sampling at the start of every patient's inflammatory process could not be made.

Our study, despite not being statistically significant, had stated lower HIF-1a levels among survivors. This could have been attributed to a possible type II error, patient sample size limitation or related to the time of sampling. Indeed, sampling time compared to the initial infection might have played a role in the predominance of either pro-inflammatory or anti-inflammatory processes of HIF-1a.

A study made by Tian et al.[17] supports the aggravating role of HIF-1a among COVID-19 patients, especially among the elderly population. Another study made by Deveci et al,[20] while reporting similar results, also supports the assumption that patients with a low HIF-1a may be actually caused due to inadequate increase in HIF-1a as a sign of systemic and clinical collapse. Thus lower HIF-1a could have also been accepted as a risk factor. Conflicting results of these studies may arise from the study population, the severity of the disease upon sampling, and the sampling time. This dual nature of the HIF-1a is further affected by the genetic background of the patients, as seen in Ljujic et al.[21] study, in which HIF-1a gene polymorphism was reported to affect thrombocytopenia in COVID-19 patients.

A protective role of HIF-1a had been reported in the study of Devaux and Raoult,[22] in which altitude and HIF signaling pathway were investigated. Altogether, we may state that, similar to what we found in our study, HIF-1a may have both protective and detrimental effects on COVID-19 patients, and

Table 5. Correlation between HIF-1a and inflammatory parameters

Parameters		HIF-1a	BNP	Troponin	D-dimer	PRC	CRP	Ferritin	IL-6
HIF-1a	CC		-0.054	-0.062	0.006	0.211	0.119	-0.038	-0.161
	p value		0.647	0.594	0.959	0.067	0.310	0.748	0.173
BNP	CC	-0.054		0.559	0.464	0.067	0.060	0.143	0.138
	p value	0.647		0.001	0.001	0.577	0.621	0.238	0.258
Troponin	CC	-0.062	0.559		0.411	0.307	0.112	0.045	0.163
	p value	0.594	0.001		0.001	0.007	0.341	0.707	0.170
D-dimer	CC	0.006	0.464	0.411		0.342	0.123	0.115	-0.024
	p value	0.959	0.001	0.001		0.003	0.308	0.350	0.847
PRC	CC	0.211	0.067	0.307	0.342		0.469	0.278	0.045
	p value	0.067	0.577	0.007	0.003		0.001	0.018	0.708
CRP	CC	0.119	0.060	0.112	0.123	0.469		0.29	0.170
	p value	0.310	0.621	0.341	0.308	0.001		0.013	0.150
Ferritin	CC	-0.038	0.143	0.045	0.115	0.278	0.29		0.294
	p value	0.748	0.238	0.707	0.350	0.018	0.013		0.013
IL-6	CC	-0.161	0.138	0.163	-0.024	0.045	0.170	0.294	
	p value	0.173	0.258	0.170	0.847	0.708	0.150	0.013	

The correlation analysis between parameters was done using Spearman Rho correlation. CC: Correlation coefficient, HIF-1a: Hypoxia-inducible factor 1-alpha, BNP: Brain natriuretic peptide, PRC: Procalcitonin, CRP: C-reactive protein, IL-6: Interleukin-6

establishing an exact cut-off may be difficult even with further studies due to the sampling time and other contributing factors.

Limitations

The study's main limitation was the lack of an initial HIF-1a level in patients before COVID-19 history. Such a limitation is not expected to be overcome easily. As in optimal conditions, a population would have been studied with basal inflammatory markers, and during the follow-up period, those who had the requirement for COVID-19-related hospital admission would be re-evaluated. This limitation was also present, in another form, regarding a lack of repeated testing, which was another possible approach to evaluate the dynamic roles of HIF-1a, especially regarding the time of pro or anti-inflammatory role.

In a similar approach, this study was limited to patients who required hospital admission after an initial emergency department evaluation. It is possible that patients whose evaluation was performed on an out-clinic basis could have provided us with different results.

The main bias in this study was related to selection. The patients in the study had hospitalization requirements, hence limiting the study population to those whose condition warranted emergency care. This limitation could not be reduced per the study design, as the investigation was to be performed on those evaluated in an emergency care setting.

CONCLUSION

Further studies with more extended follow-up periods and participants are required to evaluate the role of HIF-1a in COVID-19 patients. Studies that include a rapid testing of inflammatory markers and repeated HIF-1a testing might illuminate the exact role and time of effect regarding HIF-1a's regulatory functions. In addition to repeated testing, sampling of HIF-1a in tissue expression might have also provided a different outlook to its possible roles. While HIF-1a could not be utilized as an independent marker in our study, its utilization with other inflammatory markers, such as BNP or IL6 may be a topic of interest in future investigations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Clinical Researches Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision No: 111/08).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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